UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: March 24, 2000

MEMORANDUM

SUBJECT: Oxamyl (PC Code 103801): HED's Response to Comments Submitted During 30-Day Registrant Error Correction Period. DP Barcode D264205.

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INTRODUCTION:

The Health Effects Division (HED) acknowledges the comments received from DuPont during the 30-day registrant error correction period for oxamyl (C. Baer letter; 2/18/00). Attached are HED's responses to the comments submitted by DuPont. Where applicable, DuPont's comments have been incorporated into HED's revised disciplinary chapters. Input has been provided by Guruva Reddy (toxicology), John Punzi (dietary exposure and residue chemistry), Ken Dockter (product chemistry), and Renee Sandvig (occupational exposure).

I. PRODUCT CHEMISTRY: (K. Dockter memo; 06/14/99)

HED acknowledges DuPont's comment (1) on the product chemistry chapter. HED agrees that the correct melting point of oxamyl is 97-100 C. The product chemistry chapter has been revised accordingly.

II. RESIDUE CHEMISTRY: (J. Punzi memo; 11/05/99)

HED acknowledges DuPont comments (1) through (5) on the residue chemistry chapter. The comments have been taken into consideration and the residue chemistry chapter has been revised accordingly.

III. ANTICIPATED RESIDUES AND ACUTE AND CHRONIC DIETARY EXPOSURE: (J. Punzi memo; 12/22/99)

HED acknowledges DuPont comments (1), (3), and (5) on the dietary exposure chapter. The comments have been taken into consideration and the dietary exposure chapter has been revised accordingly. HED's responses to DuPont comments (2) and (4) are as follows:

2. DuPont's Comment:

On page 6, second paragraph, it states the Agency has used a 24-hour period for consumption in the acute dietary analysis. It has been demonstrated that rats' cholinesterase levels reach normal levels two hours after ingestion of oxamyl. We believe the acute dietary risk calculations need to be viewed in two-hour increments rather than over 24 hours.

HED's Response:

The Agency currently uses 24-hour food consumption estimates for exposure calculations, since the current methods in use for dietary exposure analysis do not allow a multiple eating event analysis to be performed. It is reasonable to assume that food items potentially containing oxamyl could be consumed at one sitting, rather than multiple times over the course of 24 hours. For example, it is possible that 250 g of apple could be consumed at one time; however, we acknowledge that it is not unreasonable for an individual to consume 250 g of apple via multiple exposures such as: apple sauce in the morning, fresh apple(s) during the day, and apple pie in the evening. Our present methods do not distinguish between the single exposure event and the multiple exposure event, and a sum of the exposures from the various food forms consumed in 24 hours is the consumption value.

4. DuPont's Comment:

On page 11, the eggplant residue data are discussed. Both tomato and peppers have PDP and/or FDA monitoring data. The Agency's memorandum "Translation of Monitoring Data" dated March 26, 1999 states that tomato or bell pepper monitoring data should be translated to all other crop group 8 commodities. This has not been done for eggplant.

HED's Response:

The translation of pepper or tomato data to eggplant would be inappropriate in this case because the use profiles are not similar. Oxamyl can be used on pepper at the rate of 6 lb ai/A and 7-day PHI; tomato directions specify 12 lb ai/A and a 3-day PHI. Oxamyl on eggplant can be used at 6 lb ai/A and a 1-day PHI.

Additional Comments on the Anticipated Residues and Acute and Chronic Dietary Exposure Chapter:

2. DuPont's Comment:

We note the following studies were not cited and were apparently not considered in preparation of this chapter. We believe each of these studies to be important to conducting realistic risk estimates of dietary exposure: carbamate market basket study; methomyl processing studies, apple washing, peeling, and cooking study; lettuce washing and trimming study; citrus washing and peeling study; and a green bean canning study.

HED's Response:

The carbamate market basket study will be reviewed when it is complete and considered for anticipated residue estimates.

Residue reduction for methomyl from the apple study (MRID 42810701) was considered appropriate to translate the oxamyl for baking only. The PDP data used for the assessment is from washed and cored apples and it would be inappropriate to add a residue reduction factor due to washing to this data. We translated the residue reduction study to all commodities with baked food forms.

It is not appropriate to translate lettuce washing and trimming study (MRID 42810702) to any of the crops that oxamyl is used on, and therefore this study was not considered.

Since all forms of citrus were non-detects, the methomyl citrus washing and peeling study (MRID 42896901) was not used.

Processing studies demonstrating methomyl reduction in processed green beans (MRID 42896902) was considered appropriate to translate to all canned forms of canned commodities.

IV. PESTICIDE POISONING INCIDENT DATA: (V. Dobozy memo; 10/01/96)

DuPont states that the preliminary incident data alleging that oxamyl played a role in the death of four cows needs to be removed as it is not factual information. Supplemental information submitted by the registrant on March 26, 1993 notes that preliminary information was incorrect and only two cows died. The two other cows survived and exhibited signs of toxicity for two days after the exposure, which is not consistent with poisoning by a carbamate, such as oxamyl.

HED is in receipt of the supplemental information submitted by DuPont that notes the death of only two cows. The data will be reviewed at a future date. Any necessary revisions to the Pesticide Incident Data report will be made at that time.

V. FQPA SAFETY FACTOR COMMITTEE CHAPTER: (B. Tarplee memo; 09/13/99)

The information in the FQPA Committee memo was provided to the Committee at the time of the FQPA Safety Factor Committee meeting. In the comments on the oxamyl preliminary RED chapter and risk assessment (February 18, 2000; pg. 6 of 23), DuPont identified the reported maximum application rate for pineapple to be an error. However, this error does not impact the final recommendation of the safety factor for oxamyl.

VI. HAZARD IDENTIFICATION ASSESSMENT REVIEW COMMITTEE REPORT: (G. Reddy memo; 08/31/99)

HED acknowledges DuPont comments (1), (2), (4), (6), (9), and (10) on the Hazard Identification Assessment Review Committee Report. The comments have been taken into consideration and the HIARC document has been amended accordingly. HED's responses to comments (3), (5), (7), and (8) are as follows:

3. DuPont's Comment:

On page 7, the committee discusses the selection of the chronic reference dose (RfD). We disagree that an acute NOEL should be used for a chronic endpoint. We believe the NOEL from the chronic dog study to be 1.36 mg/kg/day and the RfD would then be set at 0.0136 mg/kg/day. We also believe that the lack of measurement of cholinesterase at time of peak effect in the chronic studies is irrelevant for setting a chronic reference dose. We also disagree with the conclusion in this section that the chronic dog NOEL is 0.9 mg/kg/day

HED's response:

HED does not consider that the selection of the acute NOAEL from the acute neurotoxicity study for chronic reference dose (RfD) and establishment of the NOAEL of 0.9 mg/kg/day from the chronic toxicity study in dog be an error. As a matter of science policy of the HIARC, a chronic RfD cannot be lower than the acute RfD. That is, one cannot accept higher levels of repeated exposure than one would accept for a single exposure. EPA considers the chronic exposure as a repeated acute exposure either in bolus or continual feeding. Hence, the chronic RfD cannot be established higher than an acute RfD. Therefore, the acute neurotoxicity NOAEL of 0.1 mg/kg/day selected for chronic RfD will remain.

Further, the Agency does not concur with the registrant's conclusion that the chronic NOAEL in male dogs should be 0.9 mg/kg/day. The registrant states that 20% brain ChE inhibition at 50 ppm dose in cerebellum is not biologically relevant because it lacks dose-response, lacks correlation with ChE activity in other brain regions, and there is great variability between the brain compartments and individual measurements. It is the policy of the Agency that 20% ChE inhibition in any one compartment is biologically relevant. In this study not only the brain ChE was inhibited (≈ 20%), but the red blood cell ChE was also inhibited. The red blood cell ChE levels were decreased 31, 22, 18, and 22%, at 13, 26, 39 and 53 week measurements compared to the controls. The RBC ChE inhibition was statistically significantly depressed at 13 and 53 weeks. In addition, at the same dose, in a separate chronic study in dogs (MRID 41697901), there was a statistically significant depression of plasma ChE at 6, 9, and 12 months by 33, 34, and 32% respectively, compared to controls in male dogs. Brain ChE was inhibited by 17% in male dogs compared to controls. Since in this study (42052701) there was ChE inhibitions in brain and as well as in red blood cell compartment and in other study (MRID 41697901) brain and plasma ChE depression occurring at the same dose levels, the Agency cannot rule out this effect as ubiquitous. Therefore, the chronic dog NOAEL in male dog remains 0.9 mg/kg/day (50 ppm).

5. DuPont's Comment:

On page 10, in section 5, "Inhalation Exposure," the endpoint is selected based on a NOEL from the acute oral neurotoxicity study. This decision does not conform to the Agency's guidance document, "The Toxicity Endpoint Selection Process", J. Rowland, February 1997.

HED's Response:

The Agency has considered the point-of-view presented above by the registrant and concluded that the acute oral neurotoxicity endpoints selected for inhalation exposure remain. We disagree with the registrant's rationale for using the LC_{50} inhalation study for inhalation endpoint because:

1. In the acute 4-hour inhalation LC_{50} study (MRID 00066902) using technical, only males were exposed. There was a dose-related increase in mortality observed at four (4) highest doses. At the lowest dose (0.02 mg/L), there was no mortality, but clinical signs associated with cholinesterase inhibition were observed. In this study 0.02 mg/L was considered the LOAEL. There was no NOAEL in the study.

2. In the one-hour inhalation study (MRID 00066903) with technical both male and female rats were exposed. There was a dose-related increase in mortality observed in three (3) highest dose in males and in all doses in females. Females were considered more sensitive than males, since 1/5 females at the lowest dose (0.10 mg/L) died following exposure. Clinical signs indicative of ChE inhibition were observed in both sexes at all dose levels. The lowest dose in males (0.14 mg/L) and females (0.10 mg/L) was considered the LOAEL. A NOAEL was not established in this study for either sex.

3. In the 4-hour LC_{50} inhalation study (MRID 40606504) with 42% formulation males and females were exposed. As in the above study, females were more sensitive than males. The mortality was steep and dose-related. There was no mortality in lowest two doses in males, but the mortality in females was observed in all but the lowest dose. Clinical signs of ChE inhibition were observed in both sexes at the lowest dose tested (0.023 mg/L). The LOAEL was the lowest dose (0.023 mg/L) tested in both sexes. No NOAEL was established for this study.

4. In view of steep dose-related mortality in both sexes, especially in females, and the fact that the NOAEL was not established in any of the LC_{50} studies, the Agency does not believe that using the LOAEL would be sufficiently protective. Therefore, acute oral neurotoxicity endpoints used earlier remain.

5. In contrast, the ODM acute inhalation study, at the lowest two doses mortality was not observed in either sex. The Agency has high confidence in this study, because the study was well conducted and conformed to the guidelines. In this study a NOAEL was established.

7. DuPont's Comment:

On page 14 in the "Chromosomal Aberration" section, it states "the test was negative up to cytotoxic concentration ($\leq$70 μg/mL -S9....)." The study actually showed the test was negative up to cytotoxic concentrations ($\leq$100 μg/mL -S9).

HED's Response:

HED does not consider this statement to be an error. The statement "test was negative up to cytotoxic concentrations ($\leq$70 μg/mL -S9)" will remain. The study report indicated that at concentrations of 23.3 μg/mL or more, there was reduction in cell confluence in cultures treated with the test article. At 70 μg/mL, cell confluence was reduced to half that of the negative or solvent controls. At 233 μg/mL there was severe toxicity, and no mitotic cells were seen. Complete lethality was found at 700 μg/mL. Study repeated with narrower dose range did not increase the incidence of dicentrics observed at 2.3 μg/mL in the first study, and the results were comparable to those of the negative and solvent controls. Based on these results, the Agency

concluded that "test was negative up to cytotoxic concentrations (≤70 μg/mL -S9)."

8. DuPont's Comment:

On page 14 in the "Other Mutagenic mechanisms" section for the in vitro unscheduled DNA synthesis in primary rat hepatocytes, it states "the test is negative up to cytotoxic concentrations (≤5 nM)." It should read, "the test is negative up to cytotoxic concentrations (≤10 mM)."

HED's Response:

The Agency acknowledges the error expressing the dose as "nM" instead of "mM." The units of expression will be changed. The statement regarding "the test was negative up to cytotoxic concentrations (≤5mM)" will remain. This is because the study results show that cytotoxicity was found in 5.0 and 10.0 mM concentrations.

VII. OCCUPATIONAL EXPOSURE CHAPTER (R. Sandvig memo; 12/28/99)

HED acknowledges DuPont comments (1) through (7) on the Occupational Exposure and Risk Assessment chapter. Comment (1) has already been addressed in Section VI of this document. HED's responses to DuPont comments (2) through (7) are as follows:

2. Dupont's Comment:

Page 7, Handler Exposures and Assumptions - The Agency does list our current label PPE correctly. However, later in Table 4, MOE's with additional PPE, the MOE's are calculated without consideration of the use of a chemical-resistant apron and/or headgear. The use of a chemical-resistant apron by mixer/loaders should provide at least as much additional protection as another layer of clothing (50%). Chemical resistant headgear should provide applicators with some additional level of protection.

HED's Response:

HED agrees that a chemical resistant apron and headgear may reduce pesticide exposure. This clothing is often added to protect against accidental exposures. Hands and arms, the areas most often exposed to pesticides during mixing and loading, are not protected by an apron or headgear. A protection factor has not been established by the Agency for these two types of protective clothing; therefore, occupational exposure risk estimates are not quantitatively reduced to take this protective clothing into account.

3. Dupont's Comment:

In the same action, it notes that "calculations of handler scenarios are completed using the

maximum application rates on the available oxamyl labels". However, in Table 3 the rate used for aerial application to curcubits (4lbs ai/acre) is a soil rate. Ground rigs traditionally do soil applications. The highest aerial application rate on our label is 3 pounds of oxamyl per acre applied to mint.

HED's Response:

Table 3, footnote (d) does specify that for aerial/chemigation equipment curcubits, ginger, and pineapples were assessed at a 4 lb ai/acre rate and mint at a 3 lb ai/acre rate. HED agrees that curcubits and ginger at 4 lb ai/acre rates are both soil applications and would not be applied aerially. However, the pineapple application can be applied by chemigation at the 4 lbs ai/acre rate. The highest aerial rate is the 3 lb ai/acre for mint and the highest chemigation rate is 4 lbs ai/acre for pineapples. The aerial/chemigation mixing/loading scenario will be assessed at the following application rates: 1 lb ai/acre for cotton, 3 lb ai/acre for mint, and 4 lbs ai/acre for pineapples, specifying in footnote (d) that the 4 lbs ai/acre rate is only for chemigation on pineapples. The aerial application and flagger scenarios will be assessed at the following application rates: 1 lb ai/acre for cotton and 3 lb ai/acre for mint.

4. Dupont's Comment:

Page 8, first paragraph - The Agency has used 1200 acres as the default acreage for aerial treatment of cotton. However, the HED Science Advisory Council for Exposure, Policy #9 document states that 1200 is the "upper range" number of acres that could be treated. We believe 350 acres should be used. It is unlikely that any aerial applicators would mix/load and apply oxamyl exclusively on any given day; and therefore would be unlikely to load the amount of oxamyl necessary to treat 1200 acres of cotton. We believe 350 acres is a much better estimate of amounts of oxamyl to which an aerial handler would be exposed. Also, the Agency has been using 350 acre treated per day aerially in almost all OP insecticide RED's, some which would be market place alternatives to oxamyl. The Agency should be consistent in the assumptions used for these risk assessments.

HED's Response:

Presently, the Science Advisory Council on Exposure is revising the acres treated per day policy. The assessment did not assess mixing/loading and applying activities together. They are assessed as separate activities, assuming that one person may mix and load oxamyl for 1200 acres of cotton or they may apply oxamyl to 1200 acres of cotton. Since cotton is a large crop, HED uses 1200 acres/day as a reasonable high end value for the mixing/loading or applying oxamyl aerially.

5. Dupont's Comment:

Page 14, Table 5 - The Agency notes in footnote (b) that closed mixing/loading systems provide a 98% protection factor. Yet, the inhalation unit exposure numbers found in Table 5 for

mixing/loading are not 98% more protective that the baseline case (1.2 ug/lbs ai vs 0.083). A different data set from PHED has been used here than in the baseline case (Table 3) resulting in protection factor much lower than 98%. It appears as if PHED closed system data from emulsifiable formulations have been used. We have not been able to identify the source of the PHED closed system trials, but assume they are products that are volatile, such that the inhalation exposure is 3.5 times higher than when the 98% protection factor is used. Such data would not provide a reliable assessment of inhalation exposure to oxamyl in a closed system because of oxamyl's low vapor pressure (3.8 x 10-7 mm Hg). In the absence of appropriate surrogate data, the use of a default protection factor (98%) is more appropriate.

HED's Response:

For the closed mixing/loading systems, a separate study from PHED was used; therefore, a 98% protection factor was not applied to baseline data. The statement in footnote (b) of Table 5 that states a 98% protection factor is incorrect and will be removed in the revised assessment. No oxamyl specific studies exist for the mixing and loading of the liquids, so PHED data was used as surrogate data. Only an oxamyl specific mixing and loading study would be able to take the chemical's volatility into account.

6. Dupont's Comment:

Page 19, Post-Application Exposure - We strongly disagree with the half lives the Agency has calculated based on the best-fit regression of the dissipation data in our three dislodgeable foliar residue studies. The Agency has chosen to fit the data with a linear regression using log transformed concentration data that assumes first order kinetics over the entire frame of the studies. We believe the data should be fit to a non-linear equation that will account for the initial rapid degradation. Using non-linear curve fit the half-life of oxamyl on foliage is 1-3 days and 5 days in soil.

The data from the date of application to the date when the residues approach the LOQ is the most significant data for the purpose of determining a re-entry interval. The long tail of additional data points just above the LOQ is not needed to establish a safe re-entry period. In a linear fit with log transformed data the residues at or close to the LOQ from days 5-28 or 35 are weighted as heavily as the data over the 1-5 day period. As a result the initial rapid decline of oxamyl on foliage, which reduces the residue to 0.1 of the initial value by day 5, is masked by the curve fitting routine. A non-linear fit weights the initial data points more heavily and gives a better description of the decline in oxamyl residues during the critical period when the residues are at a concentration of concern in the evaluation of worker safety. The non-linear curve fitting approach has been advocated by USEPA EFED for determination of pesticides half-lives in soil when the decline curve clearly do not fit a linear first order curve fit. Concurrent with this letter we are submitting supplemental reports for our three dislodgeable foliar residue studies. Using our dissipation data results in re-entry intervals shorter than currently in the draft chapter.

HED's Response:

HED has examined the supplemental reports submitted on the three dislodgeable foliar residue studies. HED determined the dissipation rates from the three dislodgeable residue studies by linear regression using log transformed concentration data that assumes first order kinetics according to the 875.2900 guidelines. The guidelines state that other models may be used to determine dissipation rates if they are adequately explained or justified. HED does not believe that enough justification has been given to show that the dissipation rates should be determined using a second order or non-linear fit to the data. The following is a list of additional reasons why HED will not change oxamyl's calculated restricted entry intervals at this time:

- In DuPont's assessment, the data was not corrected to account for the field recovery. Data points were corrected for field recovery in the HED assessment to account for the low reported field recoveries.

- The DuPont assessment also considered data points below the "safe reentry level" irrelevant and removed before determining the dissipation rate. All data points above the limit of detection should be included to determine the dissipation rate over the entire length of the study.

- Not enough information was given in the reports to reproduce the fitted data results provided in the DuPont response.

7. Dupont's Comment:

Page 20, Assumptions - We believe the transfer coefficients used as default values are overly conservative. The Agency recently published a RED for an OP where much lower transfer coefficients were used. The Agency has stated in the past that transfer coefficients are a function of work activity, not the chemical involved. In addition, new data from the Agricultural Reentry Task Force indicates that the actual transfer coefficient for harvesting of tree fruit is much lower. Using similar transfer coefficients would result in oxamyl maintaining its present 48 hour re-entry interval.

HED's Response:

HED used standard values for the transfer coefficients from the Exposure Science Advisory Council Policy, which is based on published literature studies, submitted guideline studies, and best professional judgement. Oxamyl specific data on transfer coefficients were not available. Data from the Agricultural Reentry Task Force are still being submitted to the Agency.

VIII. Health Effects Division Chapter (C. Jarvis memo; 12/30/99)

HED acknowledges DuPont comments (1), (2), (4a), (4b), (4d), and (7) on the HED chapter. The comments have been taken into consideration and the HED chapter has been revised accordingly. DuPont comments (4c), (4e), (4f), (5), and (6) on the HED chapter have already been addressed in Section VI of this document. HED's response to DuPont comment (3) is as follows:

3. DuPont's Comment:

On page 5, section 3.1 "Hazard Profile," second paragraph states that higher NOELs were seen in the chronic studies verus the acute neurotoxicity study. EPA notes that the acute neurotoxicity endpoint is lower than that of the subchronic neurotoxicity endpoint as well as those of the chronic rat and dog studies. The Agency notes that in the subchronic and chronic toxicity studies, cholinesterase inhibition was not measured at the time to peak effects, implying that this is the reason for differences in endpoints. DuPont disagrees with this interpretation and instead believes that the greater sensitivity in the acute neurotoxicity study has more to do with how the material is administered.

HED's Response:

The Agency is aware of the differences in cholinesterase endpoints in acute oral (bolus) vs subchronic/chronic feeding studies, however, as a matter of science policy of the HIARC, a chronic RfD cannot be lower than the acute RfD. That is, one cannot accept higher levels of repeated exposure than one would accept for a single exposure. EPA considers the chronic exposure as a repeated acute exposure either in bolus or continual feeding. Hence, the chronic RfD cannot be established higher than an acute RfD. Therefore, the statement will remain.

VIII. Toxicology Chapter (G. Reddy memo; 10/14/99)

HED acknowledges DuPont comments (1), (3), (4), (6), (7), and (8) on the toxicology chapter. The comments have been taken into consideration and the toxicology chapter has been revised accordingly. DuPont comments (2), (5), (9), (10), and (11) on the toxicology chapter have already been addressed in Section VI of this document.